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KUNZ, G

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REBECCA R. GAUMOND
WOODCOCK WASHBURN KURTZ MACKIEWICZ
& NORRIS
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 3-13-95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 9-10 AND 15-16 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 9-10 AND 15-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Applicant's Request for Reconsideration, Supplemental Declaration, and Information Disclosure Statement filed March 13, 1995 have been received and entered into the record.

Claims 9 - 10 and 15 - 16 are pending in the case.

The previous rejection of claims 9 - 10 and 15 - 16 under 35 USC 101 has been withdrawn.

The rejections of claims 9 - 10 and 15 - 16 under 35 USC 103 as being obvious over Cotten et al. and Iribarren et al. in view of Wagner et al. are maintained. Applicant has argued that neither the Cotten et al. nor the Wagner et al. references are legitimate prior art because of applicant's earlier U.S. and PCT prior dates. This argument has been fully considered but is not deemed persuasive. In order for the examiner to determine if these obviousness rejections should be withdrawn, the applicant is requested to cite the page and lines in each of the prior applications which **fully** support all four pending claims.

Claims 15 - 16 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The specification fails to provide adequate written description in support of the limitations " C4 - C20 alkyl " and " C5 - C20 alkyl ". These limitations are deemed to be

new matter. Therefore, the instant disclosure is not enabling for these claims. THIS IS A NEW MATTER REJECTION.

Claims 9 - 10 and 15 - 16 are rejected under 35 U.S.C. § 112, first paragraph, because the specification fails to provide an adequate written description of the invention and fails to teach adequately how to make and/or use the invention, i.e. fails to provide an enabling disclosure.

Under 35 USC 112, first paragraph, the applicant is required to describe the invention in such **full clear, concise and exact terms** that the person of skill in the art could practice the invention **without undue experimentation**. The instant specification teaches the artisan how to prepare several of the specific 2'-O-modified nucleotides used in the preparation of 2'-O-modified oligonucleotides: 2'-O-propyl, 2'-O-pentyl, 2'-O-nonyl, 2'-O-octadecyl, and 2'-O-imidazolyl-butyl. However, there is no hybridization data documenting the binding affinity of oligonucleotide containing uniform 2'-O-modifications. Without such data, the person of skill in the art would not find the specification to be enabling for one to practice the invention **without undue experimentation**. The criteria for determining whether undue experimentation is actually required for the artisan to practice the invention has been clearly set forth by In re Forman 230 USPQ 546. The factors are:

1) Quantity of experimentation necessary
2) Amount of guidance presented

3) Presence or absence of working examples
4) Nature of the Invention
5) State of the Prior Art
6) Predictability of the Art
7) Breadth of the claims
8) Level of skill in the art

1. QUANTITY OF EXPERIMENTATION

With regard to factor one, the quantity of experimentation needed to determine the specific identity of the 2'-O-modified compounds which applicant intends to utilize, including the specific limitations intended to be employed via the plethora of modifications asserted to be applicable in diagnostic methods, research methods and therapeutics, would indeed require voluminous experimentation. The absence of specific disclosures delineating the identity of the diagnostic, research and therapeutic procedures in which the instant compounds are intended to be utilized invites the skilled artisan to engage in experiments to investigates the applicability of the compounds claimed in undisclosed methods and procedures.

2. GUIDANCE PROVIDED

There is little guidance given in the specification as to specific diagnostic, research and therapeutic methods the compounds of the instant invention are to be used in. There is little guidance provided as to the results of the multitude of instantly claimed modifications on the internucleoside linkages and on the nucleobase moieties as they are drawn to the preparation of polymers intended to be used in diagnostic, research or

therapeutic methods, specifically as they relate to:

1) the T_m value;
2) binding affinity;
3) stereochemical problems;
4) stability to nucleases;
5) penetration across membranes;
6) the crucial influence of secondary and tertiary structure of the polymers containing the instantly claimed monomers; and
7) the effect of the chain length of the instant monomers incorporated into polymeric structure.

3. WORKING EXAMPLES IN DISCLOSURE

The working examples are limited to methods of preparation of 2'-O-modified guanosine and 2'-O-modified 2-aminoadenosine wherein the modification may be propyl, pentyl, nonyl, octadecyl, imidazoyl-butyl, and N-phthalimido. However, is the **NO** data showing the melting temperatures (hybridization binding affinity) of a single oligonucleotide with such uniform 2'-O-modifications. The teaching of Iribarren et al. (PNAS 87: 7747, 1990) that branched 5-carbon modifications at the 2'-O-position, such as 3,3-dimethylallyl, "resulted in severe reduction in hybridization to complementary RNA sequences" (page 7750, column 2, lines 8 - 10) means that person of ordinary skill in the art would question whether many if not most of the claimed 2'-O-modifications would create a uniformly modified oligonucleotide which could specific bind to the complementary sequence of DNA or RNA to permit either simple probe usage much less use as an anti-sense inhibitor of gene expression. The specification is woefully inadequate to properly support the thousands of

different 2'-O-modifications encompassed by the claims without substantial working examples showing the effect of a wide range of 2'-O-modifications on the hybridization affinity and specificity.

4. Nature of the Invention

Modifications of nucleosides and the subsequent incorporation of such modifications into polymeric (nucleic acids structures) for diagnostic and research procedures is recognized as essential in the study of pharmacokinetics, therapeutics and antisense applications of nucleic acids. Although the art recognizes many different types and modes of modifying nucleic acids, the various physiochemical properties, stereochemical problems, specificity in binding, environmental stability, and penetration across membranes in vitro and in vivo creates an atmosphere for the necessity of extensive research in this burgeoning art area. Many diagnostic, research and therapeutic applications of nucleic acids and theory concerning such represent state-of-the-art experimentation in the field of nucleic acid chemistry as it relates to the use of DNA, RNA and analogues of same in genetics and research.

5. STATE OF THE PRIOR ART

The state of the prior art documents the use of specific nucleic acid modifications including internucleoside modifications in oligonucleotides and nucleobase modifications on

monomers oligonucleotides/ - sides. The prior art teaches the necessity for obtaining the specific identity of preselected sequences for the use of nucleic acids to effectuate hybridization in diagnostic, research and therapeutic applications. The use of various modifications and the applications of such nucleic acid chemistry is well documented, however, each modification is recognized as being based upon the use as demonstrated in the prior art, considering such factors as physiochemical properties for the specific modifications, stereochemical problems due to bulky side groups causing stearic hinderance, requirements for specificity in covalent binding, stability to nucleases, buffers, and other environmental conditions and the ability of the modified compound to traverse cellular membranes in vivo and in vitro diagnostic and experimental procedures.

6. PREDICTABILITY IN THE ART

The instant specification fails to provide the specific identity of diagnostic, research and therapeutic procedures in which the instant compounds are to be used. Without the identity of the specific diagnostic, research or therapeutic methods in which applicants intent to employ the instant compounds, the artisan could not predict how the plethora of compounds encompassed by the Markush groups would perform. This art does not extrapolate the intended usefulness of compounds based upon

the mere interchangeability in chemical synthesis of moieties with predictability in diagnostic, research or therapeutic methods with regard to monomeric nucleoside or nucleotide compounds, wherein said monomers are polymerized with inter-nucleoside modifications or nucleobase modifications. Each modification which creates a different compound also creates a compound which will have different properties in the specific diagnostic and research environments in which these compounds are to be employed.

7. BREADTH OF CLAIMS

The claims encompass thousands if not hundreds of thousands of different compounds whose members possess a wide range of sizes, wide range of hydrogen bonding potentials, wide range of aromaticity, and a wide range of hydrophobicity/hydrophilicity. Without clear and specific guidance the person of ordinary skill in the art would not know which 2'-O-modifications to choose for optimal hybridization binding affinity, not would he know how many of such modifications to use in any given oligonucleotide or where to place such modifications within the oligonucleotide.

8. RELATIVE SKILL IN THE ART

The relative skill in the art as it relates to preparation of modified nucleosides and modified nucleoside phosphate monomers as well as oligomeric synthesis incorporating the use of said monomers is that of a Masters level. The relative skill

in this art as it relates to diagnostic research and therapeutic applications of the modified monomers as well as their incorporation into polymeric structure is that of a Ph.D. level.

When taken as a whole, the above analysis of the criteria for undue experimentation as set forth in Forman makes it clear that the instant specification is not enabling for the scope of the invention. Applicants should claim that which is commensurate in scope with the invention as set forth in the instant disclosure.

The Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves, see In re Gardner et al. 166 USPQ 137 (CCPA 1970).

The applicant argues against the lack of enablement rejection on the grounds that "there is no reason to believe, in view of the Iribarren, et al. reference that the claimed compounds will not hybridize to some measurable extent. . . ." The Iribarren et al. reference teaches that a five carbon 2'-O-modification (3,3-dimethylallyl) "resulted in severe reduction in hybridization to complementary RNA sequences (page 7750, column 2, lines 8 - 10). However, the claims encompass even much larger and bulkier groups such as naphthalene (carbocycle) and all isomers of C20 alkyl and C20 alkenyl and C20 alkynyl. The article by Guinosso et al.

cited by applicant does teach that 2'-O-nonyl modifications actually increased the melting temperature of the resulting hybrid. These arguments have been fully considered but are not deemed persausive. The 2'-O-nonyl group used in the Guinosso et al. reference was a straight chain alkyl group, not a bulky branched alkyl group. This information is not commensurate with the scope of the claims which reads on thousands of various modifications at the 2'-O-positions.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kunz, whose telephone number is (703) 308-4623. The examiner can normally be reached on Tuesday through Friday from 6:30 AM to 4:00 PM. The examiner can also be reached on alternate Mondays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Robinson, can be reached on (703) 308-2897. The fax phone number for this Group is (703) 305-3230.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Gary L. Kunz
PATENT EXAMINER
GROUP 1800

Gary L. Kunz, Ph.D.
July 18, 1995